Amendments to the Specification:

Please delete the paragraph bridging pages 9-10 of the specification and replace it with the following paragraph:

If the hyaluronic acid starting material is a hydrophobic solid, such as ~~Hyaff-11®~~ HYAFF-11®, the hyaluronic acid is first solubilized in an organic solvent to form a solution. The organic solvent may be any pharmaceutically acceptable solvent, such as N-methylpyrrolidone (NMP) or dimethyl sulfoxide (DMSO), preferably NMP. The solution may comprise between about 1 and about 50 % (w/v) hyaluronic acid, preferably between about 5 and 20 % (w/v), and most preferably about 10 % (w/v) hyaluronic acid. The dry powdered osteogenic protein is dispersed in the hyaluronic acid solution at a concentration of between about 1 and about 50 % (w/w), preferably about 20 % (w/w), and optional excipients (e.g., amino acids, sugars, salts, surfactants, polymers, etc.) are added at a concentration of between about 1 and about 50 % (w/w), preferably between about 20 and about 40 % (w/w). The compositions of the invention may further comprise a bone resorption inhibitor, which may be included in the mixing step in dry powder or soluble form, individually or in combination with the osteogenic protein component.

Please delete the first full paragraph on page 10 of the specification and replace it with the following paragraph:

If the hyaluronic acid starting material is in a hydrophilic form, such as ~~Hyaff-11p65®~~ HYAFF-11P65®, the hyaluronic acid may be blended with an aqueous buffer comprising optional excipients until the mass assumes a paste-like consistency. The

paste-like substance may comprise between about 1 and about 40 % (w/v), preferably between about 5 and about 30 % (w/v), and more preferably between about 15 and about 20 % (w/v) hyaluronic acid. In an exemplified embodiment, the paste-like substance comprises 18.75 % (w/v) hyaluronic acid. The dry powdered osteogenic protein is then mixed into the hyaluronic acid paste prior to shaping. Alternatively, rather than blending with an aqueous buffer comprising optional excipients, the hyaluronic acid starting material may be blended with an aqueous buffer comprising soluble osteogenic protein with optional excipients until the mass assumes a paste-like consistency or a viscous liquid or gel appearance. The compositions may further comprise a bone resorption inhibitor, which may be included in the mixing step in dry powder or soluble form, individually or in combination with the osteogenic protein component.

Please delete the paragraph bridging pages 10-11 of the specification and replace it with the following paragraph:

Once the components have been combined and blended into a paste or viscous liquid or gel, the osteogenic material is packed into a cylindrical mold, air or gas-permeable tubing (e.g., silastic or ~~Teflon®/FEP~~ TEFLON®/FEP), or extrusion type apparatus, such as a syringe. If a syringe is used for the forming step, the plunger of the syringe is inserted and a sufficient amount of pressure is applied to extrude a continuous length of paste onto a dry surface, in the case of water soluble hyaluronic acid. In the case of water insoluble hyaluronic acid, a continuous length of gel is extruded into a nonsolvent bath enabling precipitation of the material. Sections are then

cut using a cutting tool such as a razor, scalpel, knife or the like, to form injectable, rod-shaped compositions. After sectioning, the rod-shaped compositions are dried, for example by air drying or freeze drying.

Please delete the paragraph bridging pages 15-16 of the specification and replace it with the following paragraph:

In an illustrative embodiment, the hyaluronic acid is an ester of hyaluronic acid with aliphatic, aromatic, aroaliphatic, cycloaliphatic or etherocyclic alcohols, in which all or a portion of the carboxylic groups of the acid are esterified, such as the hyaluronic acid derivatives described in U.S. Pat. No. 5,336,767, which is hereby incorporated by reference in its entirety herein. The hyaluronic acid starting materials may be as described in co-pending U.S. application Serial No. 09/687,283, filed October 13, 2000, which is hereby incorporated by reference in its entirety herein. Preferably, the hyaluronan-based starting materials are solids such as non-woven pads, felts, sheets, powders, sponges, and microspheres sold under the tradename ~~Hyaff®~~ HYAFF® by Fidia Advanced Biopolymers, Abano Terme, Italy. ~~Hyaff®~~ HYAFF® materials are described, for example, in U.S. Pat. Nos. 4,851,521; 4,965,353; and 5,202,431; and EP 0 216 453, all of which are hereby incorporated by reference in their entireties herein. The ~~Hyaff®~~ HYAFF® materials are esters of hyaluronic acid having one or a combination of ester moieties (e.g., benzyl, ethyl, propyl, pentyl, or larger molecules such as hydrocortisone or methyl prednisone), as well as various degrees of esterification (i.e., partial esters or complete esters). Partial esters of ~~Hyaff®~~ HYAFF® materials are designated by percent esterification ranging from 50-99 % (e.g., ~~Hyaff-~~

~~11p65®~~ HYAFF-11P65® and ~~Hyaff-11p80®~~ HYAFF-11P80®), while complete esters are 100 % esters of hyaluronic acid (e.g., ~~Hyaff-11®~~ HYAFF-11®). In addition to providing the desired handling characteristics of the compositions of the present invention, ~~Hyaff®~~ HYAFF® materials also provide a means for manipulating the bioavailability and absorption kinetics of the active ingredient(s) [see, e.g., U.S. Pat. Nos. 6,339,074; 6,232,303; and 6,066,340, all of which are incorporated by reference in their entireties herein].

Please delete the first full paragraph on page 20 of the specification and replace it with the following paragraph:

In one embodiment of the present invention, the excipient is present in powder form, which is then mixed with the active agent(s) into solubilized ~~Hyaff-11®~~ HYAFF-11® in organic solvent, and extruded into ethanol (nonsolvent) to form rods, which are then rinsed and dried. The final composition may contain one or a combination of excipients, preferably a salt, sugar (e.g., sucrose) and/or amino acid (e.g., glycine and/or glutamic acid). Preferred compositions of the present invention comprise about 1 to about 60 % (w/w) amino acid, about 1 to about 60 % (w/w) of a sugar, and about 1 to about 60 % (w/w) synthetic polymer. In a preferred embodiment of the invention, the formulation comprises about 20-50 % (w/w) amino acid, and/or about 5-50 % (w/w) sugar, and/or about 20-50 % (w/w) synthetic polymer.

Please delete the second full paragraph on page 20 of the specification and replace it with the following paragraph:

The injectable compositions of the present invention may be administered in any clinically acceptable manner of injection. A number of commercially available syringes may be suitable for use in the present invention, and for administration of the compositions of the present invention. For example, suitable syringes are available the ~~Calasept®~~ CALASEPT® syringe [JS Dental Manufacturing, Ridgefield CT] comprises sterile calcium hydroxide paste in isotonic saline solution, in a non-aspirating or modified aspirating cartridge syringe; ~~Henke-Ject®~~ HENKE-JECT® aspirating syringe and ~~Hypo®~~ HYPO® dental syringes/needles [Smith & Nephew MPL, Franklin Park, IL]; intraosseous needles from MPL, Inc., Chicago IL; and ~~Luer-Lok®~~ LUER-LOK® Syringes [Becton Dickinson, Franklin Lakes, NJ], may all be appropriate syringes for use in the present invention. Any syringe capable of holding and delivering an injectable rod and/or enabling extrusion with an obdurator is appropriate for use.

Please delete the heading and paragraph bridging pages 25-26 of the specification and replace it with the following heading and paragraph:

Example 1: Formulation of ~~Hyaff-11~~ HYAFF-11® Rods

Injectable 100 % esterified ~~Hyaff-11~~ HYAFF-11® rod-shaped compositions (1 mm in diameter) were prepared and evaluated for recombinant human bone morphogenetic protein-2 (rhBMP-2) retention and bone formation efficacy. The rod-shaped compositions comprised ~~Hyaff-11®~~ HYAFF-11® hyaluronan-based material as carrier, two doses (see Table 1) of rhBMP-2 as active ingredient, and varying amounts of excipients for modulation of release kinetics. Excipients used in this example consisted of dry powder forms of either glutamic acid or buffer salts. Buffer salts

contained 0.5 % sucrose, 2.5 % glycine, 5 mM L-glutamic acid, 5 mM NaCl, and 0.01 % polysorbate 80. The Hyaff-11® based compositions were formed into rod shapes using a phase inversion process. Briefly, rhBMP-2 and excipients (glutamate and buffer salts) were mixed into pre-solubilized ~~Hyaff-11®~~ HYAFF-11® particulates (10 % w/v) in organic solvent N-methylpyrrolidone (NMP), extruded into excess ethanol (nonsolvent) using a syringe and a catheter (e.g., 16-gauge), phase inverted for 1 hour, rinsed, and dried. The drying step consisted of 24 hour air-drying followed by a 24 hour lyophilization step. Extrusion was performed using a metered syringe pump, preferably at 0.2 mL/min injection rate. The following ~~Hyaff-11®~~-HYAFF-11®-based compositions were prepared: ~~Hyaff-11®~~ HYAFF-11®, 20 % (w/w) rhBMP-2, and 40 % (w/w) glutamate (i.e., 40/40/20 (w/w) ~~Hyaff-11®~~/HYAFF-11®/glutamate/rhBMP-2); ~~Hyaff-11®,~~ HYAFF-11®, 60 % (w/w) rhBMP-2/buffer salts (i.e., 40/60 (w/w) ~~Hyaff-11®~~/HYAFF-11®/rhBMP-2); and ~~Hyaff-11®,~~ HYAFF-11®, 20 % (w/w) rhBMP-2, and 20 % (w/w) buffer salts (i.e., 60/20/20 (w/w) ~~Hyaff-11®~~/HYAFF-11®/buffer salts/rhBMP-2). High rhBMP-2 doses were obtained by desalting the protein formulation prior to combination with the Hyaff-11. Dried rods were typically cut into 1 or 2 cm segments for further evaluation. The theoretical doses of the rods are listed in Table 1. The preferred mode of administration is a 16-gauge hypodermic needle equipped with an obdurator to inject the solid rods into the intraosseous site.

Please delete Table 1 on page 26 of the specification and replace it with the following table:

Table 1.

rhBMP-2 Doses for Injectable ~~Hyaff®~~ HYAFF® Rod Formulations

Formulation	Theoretical Dose (µg BMP-2/mg rod)	(mg BMP-2/cm rod)
40/40/20 (w/w) ~~Hyaff-11®~~HYAFF-11®/Glutamate/rhBMP-2	200	1.5
40/60 (w/w) ~~Hyaff-11®~~HYAFF-11®/rhBMP-2	71	0.5
60/20/20 (w/w) ~~Hyaff-11®~~HYAFF-11®/buffer salts/rhBMP-2	200	1.3
80/20 (w/w) ~~Hyaff-11p65®~~HYAFF-11P65®/rhBMP-2	200	1.2
60/40 (w/w) ~~Hyaff-11p65®~~HYAFF-11P65®/rhBMP-2	400	2.4

Please delete the heading and paragraph bridging pages 26-27 of the specification and replace it with the following heading and paragraph:

Example 2: Formulation of ~~Hyaff-11p65®~~ HYAFF-11P65® Rods

Injectable 65 % esterified Hyaff-11p65 rod-shaped compositions (1 mm in diameter) were prepared and evaluated for rhBMP-2 retention and bone formation

efficacy. The rod-shaped compositions comprised ~~Hyaff-11p65®~~ HYAFF-11P65® hyaluronan-based material as carrier and two doses (see Table 1) of rhBMP-2 as active ingredient. ~~Hyaff-11p65®~~ HYAFF-11P65®-based compositions comprising 20 % (w/w) rhBMP-2 (i.e., 80/20 (w/w) ~~Hyaff-11p65®~~HYAFF-11P65®/rhBMP-2) or 40 % (w/w) rhBMP-2 (i.e., 60/40 (w/w) ~~Hyaff-11p65®~~HYAFF-11P65®/rhBMP-2) were prepared by mixing desalted rhBMP-2 and ~~Hyaff-11p65®~~ HYAFF-11P65® non-woven pads in dry forms, followed by hydrating to 18.75 % (w/v) of the weight of the non-woven pad, mixing to a white paste-like consistency, transferring to a syringe, extruding through a catheter (e.g., 16-gauge), and drying. A variation of this method consists of extruding the paste through a catheter to a rod form, freezing the rod (in –80°C or liquid nitrogen), inserting into a slightly larger diameter tubing (e.g., 14-gauge catheter), and drying. The drying step consisted of 24 hour air-drying followed by a 24 hour lyophilization step. Alternative methods of rod preparation include molding the ~~Hyaff-11p65®~~ HYAFF-11P65® paste into a 1.5 mm inner-diameter silastic or ~~Teflon®/FeP~~ TEFLON®/FEP tubing followed by drying. The preferred mode of administration is a 16-gauge hypodermic needle equipped with an obdurator to force the solid rods into the intraosseous site.

Please delete the first full paragraph on page 27 of the Specification and replace it with the following paragraph:

All rod-shaped compositions were rigid, straight, handleable, and injectable through a 16-gauge needle. Scanning electron micrographs (SEM) of ~~Hyaff-11®~~ HYAFF-11® rod compositions were typically solid, dense, and smooth, while those of

~~Hyaff-11p65®~~ HYAFF-11P65® rod compositions were densely packed with short, fibrillar segments of the native non-woven fibers. Bioactivity of rhBMP-2 in the rod-shaped compositions was obtained after extracting rhBMP-2 from the compositions and testing its ability to induce alkaline phosphatase (a bone marker) expression in mouse W-20-17 stromal cells. The rhBMP-2 from ~~Hyaff-11®~~ HYAFF-11® and ~~Hyaff-11p65®~~ HYAFF-11P65® rod compositions were bioactive.

Please delete the paragraph bridging pages 27-28 of the Specification and replace it with the following paragraph:

A range of in vivo rhBMP-2 retention profiles were obtained using ~~Hyaff-11®~~ HYAFF-11® and ~~Hyaff-11p65®~~ HYAFF-11P65® rod compositions. Local retention times of rhBMP-2 in 1 cm rod-shaped compositions (prepared as described in Example 1 and 2) were evaluated in a rabbit distal femur intraosseous model using ^{125}I-rhBMP-2 and gamma scintigraphy (Figure 1). Formulations comprising ~~Hyaff-11®~~ HYAFF-11® (not ~~Hyaff-11p65®~~ HYAFF-11P65®) provided slow, sustained release of rhBMP-2, regardless of BMP-2 dose or excipients. Sterilization of the glutamate excipient by ethylene oxide provided a slightly more burst release during the initial 3-day period as compared to gamma-sterilized glutamate. The 80/20 (w/w) ~~Hyaff-11p65®~~HYAFF-11P65®/rhBMP-2 composition provided the fastest release kinetics of rhBMP-2.

Please delete the first full paragraph on page 28 of the specification and replace it with the following paragraph:

The ~~Hyaff-11®~~ HYAFF-11®-based compositions (not ~~Hyaff-11p65®~~ HYAFF-11P65®), prepared as described above, were evaluated for biocompatibility and effect on bone formation two weeks following subcutaneous (ventral thorax) and intraosseous (distal femur) administration in rats. The rod-shaped compositions were 2 mm and 10 mm in length for intraosseous and subcutaneous administration, respectively. Radiographic and histologic analysis of subcutaneous sites of administration showed bone formation adjacent to the rod-shaped compositions containing rhBMP-2, suggesting that rhBMP-2/~~Hyaff-11®~~HYAFF-11® rods were osteoinductive (data not shown). Both subcutaneous and intraosseous sites of administration showed minimum inflammatory responses, suggesting good biocompatibility of the hyaluronic acid/BMP-2 compositions. The ~~Hyaff-11®~~ HYAFF-11® and ~~Hyaff-11p65®~~ HYAFF-11P65® rod compositions were additionally injected into rabbit distal femurs and after 7 weeks, considerable de novo bone formation in the intraosseous space was observed by histology (data not shown) and particularly in the 80/20 (w/w) ~~Hyaff-11p65®~~HYAFF-11P65®/rhBMP-2 and 40/40/20 (w/w) ~~Hyaff-11®~~HYAFF-11®/glutamate/rhBMP-2 formulations. Injection of 80/20 (w/w) ~~Hyaff-11p65®~~HYAFF-11P65®/rhBMP-2 rod formulation into the distal radius of ovariectomized baboons resulted in a 30 % relative increase in total bone volume compared to untreated controls histologically (data not shown).